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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

NOGUEROLA, ALEXANDER STEPHAN

ART UNIT	PAPER NUMBER
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1753

DATE MAILED: 07/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/629,970

Applicant(s)

RAMSEY ET AL.

Examiner

ALEX NOGUEROLA

Art Unit

1753

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-56 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-56 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 30 July 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>01/03/2005</u> . | 6) <input type="checkbox"/> Other: ____ |

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 3, 20, and 21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make use the invention.

Claim 3 requires the "step of enclosing said nanochannel with an uncoated cover member after applying said coating material, said channel having a second depth reduced by approximately said defined thickness." Considering now the "Wand" factors (MPEP 2164.01(a)), Claim 3, a process of making claim, is very broad in some respects as it does not limit the composition of the solid substrate, the composition of the coating, how the walls of the nanochannel are formed, how the nanochannel is to be enclosed with the uncoated cover member, how the coating is to be applied to the nanochannel, the dimensions of the nanochannel, or the possible range of the defined thickness. See Claim 3 and the last two paragraph at the bottom of page 11 of the specification. Also,

Art Unit: 1753

"The invention has applicability to any nanoscale passageway, independent of how it was formed." See page 12 of the specification. The nature of the invention is one requiring sophisticated manufacturing as both the channel and the coating are to have dimensions on the order of nanometers. The state of the art is not well developed as the art of forming nanofluidic microstructures is new. As acknowledged by Applicants current manufacturing techniques are limited or have unknown capability.

With regard to manufacturing a nanochannel,

"Presently, photolithography is limited to about 100 nm or greater for defining feature size" (Page 4 of the specification);

"Clearly, photolithographic-based fabrication methods limit how small fluidic channels can be made" (Page 4 of the specification);

"In practice, ion beam milling features are typically limited to length scales of a few tens of nanometers, again considerably larger than the desired size of approximately 1 nm" (Page 5 of the specification);

"It may also be possible to use proximal probe techniques to perform lithography or to directly etch features in a substrate at eh nanometer length scale [emphasis added]" (Page 5 of the specification);

"This later work [Li et al.] forms a nanometer scale hole through a substrate rather than forming a nanometer conduit in the plane of the substrate" (Page 6 of the specification);

"As is known, sacrificial layer etching can also be used to form nanofluidic channels. However, the removal of the sacrificial layer in nano-channels is non-trivial ... Still this process involves deposition machines and is a time-consuming and complex process that requires careful control of the non-uniformity during the deposition process" (paragraph [0005] in Guo et al. (US 2003/0209314 A1)); and

"New fabrication techniques must be developed if the full potential of nanofluidics is to be realized." (Page 6 of the specification).

With regard to enclosing the nanochannel with a cover member,

'... known methods of constructing sealed "micron-scale" fluidic channels typically include anodic bonding of a glass coverslip or soft elastomeric material to prefabricated channels on a substrate. The high temperature and high voltages typically used in the anodic bonding process greatly limit the process to commercial applications; while the bonding of soft elastomeric material, such as PDMS, to nanofluidic channels being about 100nm or less in size often results in the partial or complete filling of the channel due to the rubber-like behavior of the

soft elastomeric material.” (paragraph [0004] in Guo et al. (US 2003/0209314 A1)).

With regard to forming the coating in the nanochannel,

Applicants cite several prior art references for instruction on this matter

Jirage (page 12 of the specification) coats a nanopore that is not enclosed with a cover member and that does not have a second depth;

Dubas (page 13 of the specification) form polyelectrolyte multilayers on a *flat* silicon wafer; and

U.S. Patents Nos. 5,858,195 and 6,001,229 (page 13 of the specification) do not disclose nanochannels; and

Hjerten, which is cited on page 14 of the specification, coats a tube with an inner diameter of 3 mm and one with an inner diameter of 0.2 mm. See Figures 1-3.

One with ordinary skill in the art would have a high degree of skill, but not likely in all of the manufacturing techniques contemplated by Applicants.

The level of predictability is not high. While techniques used in manufacturing and coating *microfluidic* channels were advanced and had some degree of predictability at the time of the invention, this was not the case for manufacturing nanochannels. As

Art Unit: 1753

the scale of structures approaches molecular scale new phenomena arise must be considered. As acknowledged by Applicants through the quotations above and as may be gleaned from Guo et al. manufacturing techniques applied in making a microfluidic device cannot necessarily be used to make a nanofluidic device without substantial adjustment.

Applicants provide very limited guidance. Applicants rely on various prior art references as guidance on forming the nanochannel and the coating in the nanochannel. As noted above, though, these techniques have substantial limitations. Looking closely now, for example, at some of the references cited for guidance of forming a coating in the nanochannel, in addition to the comments above on the disclosed references on forming a coating in the nanochannel, it should be noted that neither U.S. Patents 5,858,195 nor 6,001,229 appear to disclose coating even the walls of a *microchannel* by using electrokinetically driven flow. Page 14 of the specification state.

Coating reagents can also be transported through the channels to be coated by using hydraulic means. For example pressure can be applied to a reagent reservoir, attached directly or indirectly to a nanochannel, using a syringe pump or by applying a vacuum to the terminus of the nanochannel.

But Claims 3 requires enclosing the nanochannel with an uncoated cover member *after* applying the coating material. So how is pressure or a vacuum to be created in the uncovered nanochannel?

Applicants' disclosure has a strong speculative tone. For example,

Art Unit: 1753

"Channel depths, in theory, can be formed that are very shallow (a few atomic layers) but may be limited practically by cover plate bonding" (page 4 of the specification),

"A top-down approach that might be effective to form nanochannels is the use of finely focused ion beam milling" (page 4 of the specification);

"It may also be possible to use proximal probe techniques to perform lithography"
" (page 5 of the specification); and

and "This technique [U.S. Patents Nos. 5,858,195 and 6,001,229] should be effective, ..."

There are no working examples in Applicants' disclosure.

Thus, for these reasons one with ordinary skill in the art at the time of the invention would have to perform undue experimentation to practice the claimed method of reducing a cross-sectional dimension of a nano-opening in a nanostructured device.

For claim 21, note again, as stated by Guo, "... the removal of the sacrificial layer in nano-channels is non-trivial."

Art Unit: 1753

3. Claim 4 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make use the invention.

The rejection of claim 3 above under 35 U.S.C. 112, first paragraph, applies also to claim 4.

4. Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 6 requires applying a coating material having a defined thickness by ion implantation. Considering now the "Wand" factors (MPEP 2164.01(a)), Claim 6, a process of making claim, is very broad in some respects as it does not limit the composition of the solid substrate, the composition of the coating, how the coating is to be applied to the nanochannel, the dimensions of the nanochannel, or the possible range of the defined thickness. See Claim 6 and the last two paragraph at the bottom of page 11 of the specification. The nature of the invention is one requiring sophisticated manufacturing as both the channel and the coating are to have dimensions on the order of nanometers. The state of the art is not well developed as the art of forming

Art Unit: 1753

nanofluidic microstructures is new. As acknowledged by Applicants current manufacturing techniques are limited or have unknown capability.

With regard to manufacturing a nanochannel,

"Presently, photolithography is limited to about 100 nm or greater for defining feature size" (Page 4 of the specification);

"Clearly photolithographic-based fabrication methods limit how small fluidic channels can be made" (Page 4 of the specification);

"In practice, ion beam milling features are typically limited to length scales of a few tens of nanometers, again considerably larger than the desired size of approximately 1 nm" (Page 5 of the specification);

"It may also be possible to use proximal probe techniques to perform lithography or to directly etch features in a substrate at eh nanometer length scale [emphasis added]" (Page 5 of the specification);

"This later work [Li et al.] forms a nanometer scale hole through a substrate rather than forming a nanometer conduit in the plane of the substrate" (Page 6 of the specification);

"As is known, sacrificial layer etching can also be used to form nanofluidic channels. However, the removal of the sacrificial layer in nano-channels is non-trivial ... Still this process involves deposition machines and is a time-consuming and complex process that requires careful control of the non-uniformity during the deposition process" (paragraph [0005] in Guo et al. (US 2003/0209314 A1)); and

"New fabrication techniques must be developed if the full potential of nanofluidics is to be realized." (Page 6 of the specification).

Art Unit: 1753

With regard to forming the coating in the nanochannel, Applicants cite several prior art references for instruction on this matter. However, none of these references involve ion beam impanation. Jirage (page 12 of the specification) first uses electroless gold deposition to form an Au coating and the chemisorption to form a thiol linked coating inside nanochannel (see the Jirage abstract);

Dubas (page 13 of the specification) form polyelectrolyte multilayers on a *flat* silicon wafer by spin coating (see the Dubas abstract);

U.S. Patents Nos. 5,858,195 and 6,001,229 (page 13 of the specification) do not disclose nanochannels nor electrically driven coating as asserted; and

Hjerten, which is cited on page 14 of the specification, uses polymerization and coats a tube with an inner diameter of 3 mm and one with an inner diameter of 0.2 mm. See Figures 1-3.

One with ordinary skill in the art would have a high degree of skill.

The level of predictability is not high. While techniques used in manufacturing

Art Unit: 1753

and coating *microfluidic* channels were advanced and had some degree of predictability at the time of the invention, this was not the case for manufacturing nanochannels. As the scale of structures approaches molecular scale new phenomena arise must be considered. As acknowledged by Applicants through the quotations above and as may be gleaned from Guo et al. manufacturing techniques applied in making a microfluidic device cannot necessarily be used to make a nanofluidic device without substantial adjustment.

Applicants provide no guidance on forming a coating by ion implantation. Applicants rely on various prior art references as guidance on forming the nanochannel and the coating in the nanochannel.

Applicants' disclosure has a strong speculative tone. For example,

"Channel depths, in theory, can be formed that are very shallow (a few atomic layers) but may be limited practically by cover plate bonding" (page 4 of the specification),

"A top-down approach that might be effective to form nanochannels is the use of finely focused ion beam milling" (page 4 of the specification);

"It may also be possible to use proximal probe techniques to perform lithography

" (page 5 of the specification); and

Art Unit: 1753

and "This technique [U.S. Patents Nos. 5,858,195 and 6,001,229] should be effective, ..."

There are no working examples in Applicants' disclosure.

Thus, for these reasons one with ordinary skill in the art at the time of the invention would have to perform undue experimentation to practice the claimed method of reducing a cross-sectional dimension of a nano-opening in a nanostructured device by effecting the step of applying the coating by ion implantation.

5. Claim 11 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make use the invention.

Claim 1 requires the molecular film to be covalently attached to the solid substrate.

Considering now the "Wand" factors (MPEP 2164.01(a)), Claim 11, a process of making claim, is very broad in some respects as it does not limit the composition of the solid substrate, the composition of the coating, how the walls of the nanochannel are formed, how the nanochannel is to be enclosed with the uncoated cover member, how the coating is to be applied to the nanochannel, the dimensions of the nanochannel, or the possible range of the defined thickness. See Claim 11 and the last two paragraph

Art Unit: 1753

at the bottom of page 11 of the specification. Also, "The invention has applicability to any nanoscale passageway, independent of how it was formed." See page 12 of the specification. The nature of the invention is one requiring sophisticated manufacturing as both the channel and the coating are to have dimensions on the order of nanometers. The state of the art is not well developed as the art of forming nanofluidic microstructures is new. As acknowledged by Applicants current manufacturing techniques are limited or have unknown capability.

With regard to manufacturing a nanochannel,

"Presently, photolithography is limited to about 100 nm or greater for defining feature size" (Page 4 of the specification);

"Clearly photolithographic-based fabrication methods limit how small fluidic channels can be made" (Page 4 of the specification);

"In practice, ion beam milling features are typically limited to length scales of a few tens of nanometers, again considerably larger than the desired size of approximately 1 nm" (Page 5 of the specification);

"It may also be possible to use proximal probe techniques to perform lithography or to directly etch features in a substrate at eh nanometer length scale [emphasis added]" (Page 5 of the specification);

"This later work [Li et al.] forms a nanometer scale hole through a substrate rather than forming a nanometer conduit in the plane of the substrate" (Page 6 of the specification);

"As is known, sacrificial layer etching can also be used to form nanofluidic channels. However, the removal of the sacrificial layer in nano-channels is non-trivial ... Still this process involves deposition machines and is a time-consuming and complex process that requires careful control of the non-uniformity during the deposition process" (paragraph [0005] in Guo et al. (US 2003/0209314 A1)); and

"New fabrication techniques must be developed if the full potential of nanofluidics is to be realized." (Page 6 of the specification).

With regard to enclosing the nanochannel with a cover member,

'... known methods of constructing sealed "micron-scale" fluidic channels typically include anodic bonding of a glass coverslip or soft elastomeric material to prefabricated channels on a substrate. The high temperature and high voltages typically used in the anodic bonding process greatly limit the process to commercial applications; while the bonding of soft elastomeric material, such as PDMS, to nanofluidic channels being about 100nm or less in size often results in

Art Unit: 1753

the partial or complete filling of the channel due to the rubber-like behavior of the soft elastomeric material.” (paragraph [0004] in Guo et al. (US 2003/0209314 A1)).

With regard to forming the coating in the nanochannel,

Applicants cite several prior art references for instruction on this matter

Jirage (page 12 of the specification) coats a nanopore that is not enclosed with a cover member and that does not have a second depth;

Dubas (page 13 of the specification) form polyelectrolyte multilayers on a *flat* silicon wafer;

U.S. Patents Nos. 5,858,195 and 6,001,229 (page 13 of the specification) do not disclose nanochannels; and

Hjerten, which is cited on page 14 of the specification, uses polymerization and coats a tube with an inner diameter of 3 mm and one with an inner diameter of 0.2 mm. See Figures 1-3.

One with ordinary skill in the art would have a high degree of skill, but not likely in all of the manufacturing techniques contemplated by Applicants.

The level of predictability is not high. While techniques used in manufacturing and coating *micro*fluidic channels were advanced and had some degree of predictability at the time of the invention, this was not the case for manufacturing nanochannels. As the scale of structures approaches molecular scale new phenomena arise must be considered. As acknowledged by Applicants through the quotations above and as may be gleaned from Guo et al. manufacturing techniques applied in making a microfluidic device cannot necessarily be used to make a nanofluidic device without substantial adjustment.

Applicants provide very limited guidance. Applicants rely on various prior art references as guidance on forming the nanochannel and the coating in the nanochannel. Only one, Hjerten, discloses covalently attaching the molecular film to the substrate. However, as noted above, the inner diameters of the capillaries used by Hjerten are 0.2 mm and 3 mm, which are several orders of magnitude larger than a nanometer channel.

Applicants' disclosure has a strong speculative tone. For example,

"Channel depths, in theory, can be formed that are very shallow (a few atomic layers) but may be limited practically by cover plate bonding" (page 4 of the specification),

"A top-down approach that might be effective to form nanochannels is the use of finely focused ion beam milling" (page 4 of the specification);

"It may also be possible to use proximal probe techniques to perform lithography" (page 5 of the specification); and

and "This technique [U.S. Patents Nos. 5,858,195 and 6,001,229] should be effective, ..."

There are no working examples in Applicants' disclosure.

Thus, for these reasons one with ordinary skill in the art at the time of the invention would have to perform undue experimentation to practice the claimed method

6. Claim 17 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make use the invention.

Claim 17 requires applying an additional polyelectrolyte coating that has the opposite charge of the polyelectrolyte to which it is applied.

Considering now the "Wand" factors (MPEP 2164.01(a)), Claim 17, a process of making claim, is very broad in some respects as it does not limit the composition of the

Art Unit: 1753

solid substrate, the composition of the coating, how the walls of the nanochannel are formed, how the nanochannel is to be enclosed with the uncoated cover member, how the coating is to be applied to the nanochannel, the dimensions of the nanochannel, or the possible range of the defined thickness. See Claim 17 and the last two paragraph at the bottom of page 11 of the specification. Also, "The invention has applicability to any nanoscale passageway, independent of how it was formed." See page 12 of the specification. The nature of the invention is one requiring sophisticated manufacturing as both the channel and the coating are to have dimensions on the order of nanometers. The state of the art is not well developed as the art of forming nanofluidic microstructures is new. As acknowledged by Applicants current manufacturing techniques are limited or have unknown capability.

With regard to manufacturing a nanochannel,

"Presently, photolithography is limited to about 100 nm or greater for defining feature size" (Page 4 of the specification);

"Clearly photolithographic-based fabrication methods limit how small fluidic channels can be made" (Page 4 of the specification);

"In practice, ion beam milling features are typically limited to length scales of a few tens of nanometers, again considerably larger than the desired size of approximately 1 nm" (Page 5 of the specification);

"It may also be possible to use proximal probe techniques to perform lithography or to directly etch features in a substrate at eh nanometer length scale [emphasis added]" (Page 5 of the specification);

"This later work [Li et al.] forms a nanometer scale hole through a substrate rather than forming a nanometer conduit in the plane of the substrate" (Page 6 of the specification);

"As is known, sacrificial layer etching can also be used to form nanofluidic channels. However, the removal of the sacrificial layer in nano-channels is non-trivial ... Still this process involves deposition machines and is a time-consuming and complex process that requires careful control of the non-uniformity during the deposition process" (paragraph [0005] in Guo et al. (US 2003/0209314 A1)); and

"New fabrication techniques must be developed if the full potential of nanofluidics is to be realized." (Page 6 of the specification).

Art Unit: 1753

With regard to forming the coating in the nanochannel,

Applicants cite several prior art references for instruction on this matter

Jirage (page 12 of the specification) coats a nanopore that is not enclosed with a cover member and that does not have a second depth;

Dubas (page 13 of the specification) form polyelectrolyte multilayers on a *flat* silicon wafer;

U.S. Patents Nos. 5,858,195 and 6,001,229 (page 13 of the specification) do not disclose nanochannels; and

Hjerten, which is cited on page 14 of the specification, uses polymerization and coats a tube with an inner diameter of 3 mm and one with an inner diameter of 0.2 mm. See Figures 1-3.

One with ordinary skill in the art would have a high degree of skill, but not likely in all of the manufacturing techniques contemplated by Applicants.

The level of predictability is not high. While techniques used in manufacturing and coating *micro*fluidic channels were advanced and had some degree of predictability at the time of the invention, this was not the case for manufacturing nanochannels. As the scale of structures approaches molecular scale new phenomena arise must be

Art Unit: 1753

considered. As acknowledged by Applicants through the quotations above and as may be gleaned from Guo et al. manufacturing techniques applied in making a microfluidic device cannot necessarily be used to make a nanofluidic device without substantial adjustment.

Applicants provide very limited guidance. Applicants rely on various prior art references as guidance on forming the nanochannel and the coating in the nanochannel. Most particularly, as noted above, Dubas, which discusses applying polyelectrolyte multilayers, is about coating a flat substrate, not a channel, let alone a nanochannel.

Applicants' disclosure has a strong speculative tone. For example,

"Channel depths, in theory, can be formed that are very shallow (a few atomic layers) but may be limited practically by cover plate bonding" (page 4 of the specification),

"A top-down approach that might be effective to form nanochannels is the use of finely focused ion beam milling" (page 4 of the specification);

"It may also be possible to use proximal probe techniques to perform lithography" (page 5 of the specification); and

and "This technique [U.S. Patents Nos. 5,858,195 and 6,001,229] should be effective, ..."

There are no working examples in Applicants' disclosure.

Thus, for these reasons one with ordinary skill in the art at the time of the invention would have to perform undue experimentation to practice the claimed method of reducing a cross-sectional dimension of a nano-opening in a nanostructured device.

7. Claim 19 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make use the invention.

Claim 19 requires the substrate to have both the open nanochannel and a microchannel having a free space with a third cross-sectional area greater than the first cross-sectional area, the microchannel being connected to the nanochannel.

Considering now the "Wand" factors (MPEP 2164.01(a)), Claim 19, a process of making claim, is very broad in some respects as it does not limit the composition of the solid substrate, the composition of the coating, how the walls of the nanochannel are formed, how the nanochannel is to be enclosed with the uncoated cover member, how the coating is to be applied to the nanochannel, the dimensions of the nanochannel, or the possible range of the defined thickness. See Claim 3 and the last two paragraph at the bottom of page 11 of the specification. Also, "The invention has applicability to any nanoscale passageway, independent of how it was formed." See page 12 of the

Art Unit: 1753

specification. The nature of the invention is one requiring sophisticated manufacturing as both the channel and the coating are to have dimensions on the order of nanometers. The state of the art is not well developed as the art of forming nanofluidic microstructures is new. As acknowledged by Applicants current manufacturing techniques are limited or have unknown capability.

With regard to manufacturing a nanochannel,

"Presently, photolithography is limited to about 100 nm or greater for defining feature size" (Page 4 of the specification);

"Clearly photolithographic-based fabrication methods limit how small fluidic channels can be made" (Page 4 of the specification);

"In practice, ion beam milling features are typically limited to length scales of a few tens of nanometers, again considerably larger than the desired size of approximately 1 nm" (Page 5 of the specification);

"It may also be possible to use proximal probe techniques to perform lithography or to directly etch features in a substrate at eh nanometer length scale [emphasis added]" (Page 5 of the specification);

"This later work [Li et al.] forms a nanometer scale hole through a substrate rather than forming a nanometer conduit in the plane of the substrate" (Page 6 of the specification);

"As is known, sacrificial layer etching can also be used to form nanofluidic channels. However, the removal of the sacrificial layer in nano-channels is non-trivial ... Still this process involves deposition machines and is a time-consuming and complex process that requires careful control of the non-uniformity during the deposition process" (paragraph [0005] in Guo et al. (US 2003/0209314 A1)); and

"New fabrication techniques must be developed if the full potential of nanofluidics is to be realized." (Page 6 of the specification).

With regard to forming the coating in the nanochannel,

Applicants cite several prior art references for instruction on this matter

Jirage (page 12 of the specification) coats a nanopore that is not enclosed with a cover member and that does not have a second depth;

Dubas (page 13 of the specification) form polyelectrolyte multilayers on a *flat* silicon wafer; and

U.S. Patents Nos. 5,858,195 and 6,001,229 (page 13 of the specification) do not disclose nanochannels; and

Hjerten, which is cited on page 14 of the specification, coats a tube with an inner diameter of 3 mm and one with an inner diameter of 0.2 mm. See Figures 1-3.

One with ordinary skill in the art would have a high degree of skill, but not likely in all of the manufacturing techniques contemplated by Applicants.

The level of predictability is not high. While techniques used in manufacturing and coating *microfluidic* channels were advanced and had some degree of predictability at the time of the invention, this was not the case for manufacturing nanochannels. As the scale of structures approaches molecular scale new phenomena arise must be considered. As acknowledged by Applicants through the quotations above and as may

Art Unit: 1753

be gleaned from Guo et al. manufacturing techniques applied in making a microfluidic device cannot necessarily be used to make a nanofluidic device without substantial adjustment.

Applicants provide very limited guidance. Applicants rely on various prior art references as guidance on forming the nanochannel and the coating in the nanochannel. As noted above, though, these techniques have substantial limitations. Looking closely now, for example, at some of the references cited for guidance of forming a coating in the nanochannel, in addition to the comments above on the disclosed references on forming a coating in the nanochannel, it should be noted that neither U.S. Patents 5,858,195 nor 6,001,229 appear to disclose coating even the walls of a *microchannel* by using electrokinetically driven flow. Page 14 of the specification state.

Coating reagents can also be transported through the channels to be coated by using hydraulic means. For example pressure can be applied to a reagent reservoir, attached directly or indirectly to a nanochannel, using a syringe pump or by applying a vacuum to the terminus of the nanochannel.

Applicants' disclosure has a strong speculative tone. For example,

"Channel depths, in theory, can be formed that are very shallow (a few atomic layers) but may be limited practically by cover plate bonding" (page 4 of the specification),

"A top-down approach that might be effective to form nanochannels is the use of finely focused ion beam milling" (page 4 of the specification);

"It may also be possible to use proximal probe techniques to perform lithography

" (page 5 of the specification); and

and "This technique [U.S. Patents Nos. 5,858,195 and 6,001,229] should be effective, ..."

There are no working examples in Applicants' disclosure.

Thus, for these reasons one with ordinary skill in the art at the time of the invention would have to perform undue experimentation to practice the claimed method

8. Claims 22-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make use the invention.

Claims 22-24 require the "step of enclosing said nanochannel with an uncoated cover member after applying said coating material, said channel having a second depth reduced by approximately said defined thickness." Considering now the "Wand" factors (MPEP 2164.01(a)), Claim 22, a process of making claim, is very broad in some respects as it does not limit the composition of the solid substrate, the composition of the coating, how the walls of the nanochannel are formed, how the nanochannel is to be enclosed with the uncoated cover member, how the coating is to be applied to the

Art Unit: 1753

nanochannel, the dimensions of the nanochannel, or the possible range of the defined thickness. See Claim 22 and the last two paragraphs at the bottom of page 11 of the specification. Also, "The invention has applicability to any nanoscale passageway, independent of how it was formed." See page 12 of the specification. The nature of the invention is one requiring sophisticated manufacturing as both the channel and the coating are to have dimensions on the order of nanometers. The state of the art is not well developed as the art of forming nanofluidic microstructures is new. As acknowledged by Applicants current manufacturing techniques are limited or have unknown capability.

With regard to manufacturing a nanochannel,

"Presently, photolithography is limited to about 100 nm or greater for defining feature size" (Page 4 of the specification);

"Clearly photolithographic-based fabrication methods limit how small fluidic channels can be made" (Page 4 of the specification);

"In practice, ion beam milling features are typically limited to length scales of a few tens of nanometers, again considerably larger than the desired size of approximately 1 nm" (Page 5 of the specification);

“It may also be possible to use proximal probe techniques to perform lithography or to directly etch features in a substrate at eh nanometer length scale [emphasis added]” (Page 5 of the specification);

“This later work [Li et al.] forms a nanometer scale hole through a substrate rather than forming a nanometer conduit in the plane of the substrate” (Page 6 of the specification);

“As is known, sacrificial layer etching can also be used to form nanofluidic channels. However, the removal of the sacrificial layer in nano-channels is non-trivial ... Still this process involves deposition machines and is a time-consuming and complex process that requires careful control of the non-uniformity during the deposition process” (paragraph [0005] in Guo et al. (US 2003/0209314 A1)); and

“New fabrication techniques must be developed if the full potential of nanofluidics is to be realized.” (Page 6 of the specification).

With regard to forming the coating in the nanochannel,

Applicants cite several prior art references for instruction on this matter

Jirage (page 12 of the specification) coats a nanopore that is not enclosed with a cover member and that does not have a second depth;

Dubas (page 13 of the specification) form polyelectrolyte multilayers on a *flat* silicon wafer;

U.S. Patents Nos. 5,858,195 and 6,001,229 (page 13 of the specification) do not disclose nanochannels; and

Hjerten, which is cited on page 14 of the specification, uses polymerization and coats a tube with an inner diameter of 3 mm and one with an inner diameter of 0.2 mm. See Figures 1-3.

One with ordinary skill in the art would have a high degree of skill, but not likely in all of the manufacturing techniques contemplated by Applicants.

The level of predictability is not high. While techniques used in manufacturing and coating *microfluidic* channels were advanced and had some degree of predictability at the time of the invention, this was not the case for manufacturing nanochannels. As the scale of structures approaches molecular scale new phenomena arise must be

Art Unit: 1753

considered. As acknowledged by Applicants through the quotations above and as may be gleaned from Guo et al. manufacturing techniques applied in making a microfluidic device cannot necessarily be used to make a nanofluidic device without substantial adjustment.

Applicants provide very limited guidance. Applicants rely on various prior art references as guidance on forming the nanochannel and the coating in the nanochannel. As noted above, though, these techniques have substantial limitations. Looking closely now, for example, at some of the references cited for guidance of forming a coating in the nanochannel, in addition to the comments above on the disclosed references on forming a coating in the nanochannel, it should be noted that neither U.S. Patents 5,858,195 nor 6,001,229 appear to disclose coating even the walls of a *microchannel* by using electrokinetically driven flow. Page 14 of the specification state.

Coating reagents can also be transported through the channels to be coated by using hydraulic means. For example pressure can be applied to a reagent reservoir, attached directly or indirectly to a nanochannel, using a syringe pump or by applying a vacuum to the terminus of the nanochannel.

But Claims 22 requires enclosing the nanochannel with a planar cover member *after* applying the coating material. So how is pressure or a vacuum to be created in the uncovered nanochannel?

Applicants' disclosure has a strong speculative tone. For example,

Art Unit: 1753

"Channel depths, in theory, can be formed that are very shallow (a few atomic layers) but may be limited practically by cover plate bonding" (page 4 of the specification),

"A top-down approach that might be effective to form nanochannels is the use of finely focused ion beam milling" (page 4 of the specification);

"It may also be possible to use proximal probe techniques to perform lithography"
" (page 5 of the specification); and

and "This technique [U.S. Patents Nos. 5,858,195 and 6,001,229] should be effective, ..."

There are no working examples in Applicants' disclosure.

Thus, for these reasons one with ordinary skill in the art at the time of the invention would have to perform undue experimentation to practice the claimed method of reducing a cross-sectional dimension of a nano-opening in a nanostructured device.

For claim 23 also note that in regard to chemical etching Applicants merely state, "Features of similar length scale [10 nm] can then be machined in a substrate using either wet (solution) or dry (plasma) etching techniques. See page 5 of the specification.

Art Unit: 1753

For claim 24 also note that in regard to ion beam milling Applicants state this approach "*might* be effective [emphasis added]", and acknowledge, "In practice, ion beam milling features are typically limited to length scales of a few tens of nanometers, again considerably larger than the desired size of approximately 1 nm," (page 5 of the specification) and that Li et al. "forms a nanometer scale hole through a substrate rather than forming a nanometer conduit in the plane of the substrate" (page 6 of the specification).

9. Claims 34, 43, and 52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make use the invention. The rejection of claim 17, above, can largely be also applied to claims 34, 43, and 52 since the unenabled aspect of all of these claims is a coating comprising a plurality of layers of polyelectrolyte material, each layer being opposite in charge to its adjacent layer.

Art Unit: 1753

10. Claims 35 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make use the invention.

Claim 35 requires the lateral dimension of the nanometer-scale conduit to be approximately one nanometer. Considering now the "Wand" factors (MPEP 2164.01(a)), Claim 35 is very broad in some respects as it does not limit the composition of the solid substrate, the composition of the coating, how the walls of the nanochannel are formed, how the coating is to be applied to the nanochannel, the dimensions of the nanochannel, or the possible range of the defined thickness. See Claim 35 and the last two paragraphs at the bottom of page 11 of the specification. Also, "The invention has applicability to any nanoscale passageway, independent of how it was formed." See page 12 of the specification. The nature of the invention is one requiring sophisticated manufacturing as both the channel and the coating are to have dimensions on the order of nanometers. The state of the art is not well developed as the art of forming nanofluidic microstructures is new. As acknowledged by Applicants current manufacturing techniques are limited or have unknown capability.

With regard to manufacturing a nanochannel,

"Presently, photolithography is limited to about 100 nm or greater for defining feature size" (Page 4 of the specification);

"Clearly photolithographic-based fabrication methods limit how small fluidic channels can be made" (Page 4 of the specification);

"In practice, ion beam milling features are typically limited to length scales of a few tens of nanometers, again considerably larger than the desired size of approximately 1 nm" (Page 5 of the specification);

"It may also be possible to use proximal probe techniques to perform lithography or to directly etch features in a substrate at eh nanometer length scale [emphasis added]" (Page 5 of the specification);

"This later work [Li et al.] forms a nanometer scale hole through a substrate rather than forming a nanometer conduit in the plane of the substrate" (Page 6 of the specification);

"As is known, sacrificial layer etching can also be used to form nanofluidic channels. However, the removal of the sacrificial layer in nano-channels is non-trivial ... Still this process involves deposition machines and is a time-consuming and complex process that requires careful control of the non-uniformity during the deposition process" (paragraph [0005] in Guo et al. (US 2003/0209314 A1)); and

"New fabrication techniques must be developed if the full potential of nanofluidics is to be realized." (Page 6 of the specification).

With regard to forming the coating in the nanochannel,

Applicants cite several prior art references for instruction on this matter

Jirage (page 12 of the specification) coats a nanopore that is not enclosed with a cover member and that does not have a second depth;

Dubas (page 13 of the specification) form polyelectrolyte multilayers on a *flat* silicon wafer;

U.S. Patents Nos. 5,858,195 and 6,001,229 (page 13 of the specification) do not disclose nanochannels; and

Hjerten, which is cited on page 14 of the specification, uses polymerization and coats a tube with an inner diameter of 3 mm and one with an inner diameter of 0.2 mm. See Figures 1-3.

One with ordinary skill in the art would have a high degree of skill, but not likely in all of the manufacturing techniques contemplated by Applicants.

The level of predictability is not high. While techniques used in manufacturing and coating *micro*fluidic channels were advanced and had some degree of predictability at the time of the invention, this was not the case for manufacturing nanochannels. As the scale of structures approaches molecular scale new phenomena arise must be

Art Unit: 1753

considered. As acknowledged by Applicants through the quotations above and as may be gleaned from Guo et al. manufacturing techniques applied in making a microfluidic device cannot necessarily be used to make a nanofluidic device without substantial adjustment.

Applicants provide very limited guidance. What little guidance is provided actually teaches away from the claimed invention. The discussion on page 12 of the specification regarding forming nano-openings only mentions making holes of 5 nanometers, not approximately 1 nm as claimed. Also, a hole is not an open channel, with a bottom wall as required by claim 25. There is also the question of how to coat a 1 nm channel. Jirage, which is cited on page 12 of the specification, discloses "reducing the cross-sectional area from 100 nm² to 10 nm² ." This would appear to substantially, if not completely, block a 1 nm channel. Page 14 of the specification states, "A single polyelectrolyte layer has a thickness ranging from approximately 1 nm to a few tens of nanometers and multilayer film thicknesses of approximately 1 micron have been formed." This coating may not even fit into the 1 nm channel. (see related claim 34, also depends from claim 25)

Applicants' disclosure has a strong speculative tone. For example,

"Channel depths, in theory, can be formed that are very shallow (a few atomic layers) but may be limited practically by cover plate bonding" (page 4 of the specification),

Art Unit: 1753

“A top-down approach that might be effective to form nanochannels is the use of finely focused ion beam milling” (page 4 of the specification);

“It may also be possible to use proximal probe techniques to perform lithography” (page 5 of the specification); and

and “This technique [U.S. Patents Nos. 5,858,195 and 6,001,229] should be effective, ...”

There are no working examples in Applicants' disclosure.

Thus, for these reasons one with ordinary skill in the art at the time of the invention would have to perform undue experimentation to make the claimed device.

11. Claims 54-56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make use the invention.

Claims 54 require using an electrical force for modifying the coating in one way or another.

Considering now the “Wand” factors (MPEP 2164.01(a)), Claims 54-56, process of making claims, are very broad in some respects as it does not limit the composition of the solid substrate, the composition of the coating, how the walls of the nanochannel are formed, how the coating is to be applied to the nanochannel, the dimensions of the nanochannel, or the possible range of the defined thickness. See Claim 54-56 and the last two paragraph at the bottom of page 11 of the specification. Also, “The invention has applicability to any nanoscale passageway, independent of how it was formed.” See page 12 of the specification. The nature of the invention is one requiring sophisticated manufacturing as both the channel and the coating are to have dimensions on the order of nanometers. The state of the art is not well developed as the art of forming nanofluidic microstructures is new. As acknowledged by Applicants current manufacturing techniques are limited or have unknown capability.

With regard to manufacturing a nanochannel,

“Presently, photolithography is limited to about 100 nm or greater for defining feature size” (Page 4 of the specification);

“Clearly photolithographic-based fabrication methods limit how small fluidic channels can be made” (Page 4 of the specification);

“In practice, ion beam milling features are typically limited to length scales of a few tens of nanometers, again considerably larger than the desired size of approximately 1 nm” (Page 5 of the specification);

"It may also be possible to use proximal probe techniques to perform lithography or to directly etch features in a substrate at eh nanometer length scale [emphasis added]" (Page 5 of the specification);

"This later work [Li et al.] forms a nanometer scale hole through a substrate rather than forming a nanometer conduit in the plane of the substrate" (Page 6 of the specification);

"As is known, sacrificial layer etching can also be used to form nanofluidic channels. However, the removal of the sacrificial layer in nano-channels is non-trivial ... Still this process involves deposition machines and is a time-consuming and complex process that requires careful control of the non-uniformity during the deposition process" (paragraph [0005] in Guo et al. (US 2003/0209314 A1)); and

"New fabrication techniques must be developed if the full potential of nanofluidics is to be realized." (Page 6 of the specification).

With regard to forming the coating in the nanochannel,

Applicants cite several prior art references for instruction on this matter

Jirage (page 12 of the specification) coats a nanopore that is not enclosed with a cover member and that does not have a second depth;

Dubas (page 13 of the specification) form polyelectrolyte multilayers on a *flat* silicon wafer; and

U.S. Patents Nos. 5,858,195 and 6,001,229 (page 13 of the specification) do not disclose nanochannels; and

Hjerten, which is cited on page 14 of the specification, coats a tube with an inner diameter of 3 mm and one with an inner diameter of 0.2 mm. See Figures 1-3.

One with ordinary skill in the art would have a high degree of skill, but not likely in all of the manufacturing techniques contemplated by Applicants.

The level of predictability is not high. While techniques used in manufacturing and coating *micro*fluidic channels were advanced and had some degree of predictability at the time of the invention, this was not the case for manufacturing nanochannels. As the scale of structures approaches molecular scale new phenomena arise must be considered. As acknowledged by Applicants through the quotations above and as may

Art Unit: 1753

be gleaned from Guo et al. manufacturing techniques applied in making a microfluidic device cannot necessarily be used to make a nanofluidic device without substantial adjustment.

Applicants provide very limited guidance. Applicants rely on various prior art references as guidance on forming the nanochannel and the coating in the nanochannel. As noted above, though, these techniques have substantial limitations. Applicants seem to rely on an informal incorporation by reference of U.S. Patents Nos. 5,858,195 and 6,001,229 for support/explanation of for claims 54-56 (See page 13 of the specification, last paragraph); however, the examiner has not found in either patent a discussion of using electrokinetic force to coat a microchannel, let alone a nanochannel. "Mere reference to another application, patent, or publication is not an incorporation of anything therein into the application containing such reference for the purpose of disclosure as required by 35 U.S.C. 112, first paragraph. Particular attention should be directed to specific portions of the reference document where the subject matter being incorporated may be found." See MPEP 608.1(p).I.A.

Applicants' disclosure has a strong speculative tone. For example,

"Channel depths, in theory, can be formed that are very shallow (a few atomic layers) but may be limited practically by cover plate bonding" (page 4 of the specification),

"A top-down approach that might be effective to form nanochannels is the use of finely focused ion beam milling" (page 4 of the specification);

"It may also be possible to use proximal probe techniques to perform lithography

" (page 5 of the specification); and

and "This technique [U.S. Patents Nos. 5,858,195 and 6,001,229] should be effective, ..."

There are no working examples in Applicants' disclosure.

Thus, for these reasons one with ordinary skill in the art at the time of the invention would have to perform undue experimentation to practice the claimed methods

12. Note that dependent claims will have the deficiencies of base and intervening claims.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claim 43 recites the limitation "said transmembrane protein" in line 4. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

16. Claims 1, 5, 7-10, 12, 13, 15, 18, 36, 37, and 39 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Lee et al. ("Electromodulated Molecular Transport in Gold-Nanotube Membranes," J. AM. CHEM. Soc. 1002, 124, 11850-1851") ("Lee").

Addressing claim 1, Lee discloses a method of reducing a cross-sectional dimension of a nano-opening in a nanostructured device, comprising the steps of

a. providing a solid substrate including a nano-opening defined by at least one wall surface fabricated in the substrate, the nano-opening having a given first cross-

Art Unit: 1753

sectional area of nanometer-scale dimensions bounded by the at least one wall surface (note the Au nanotube in Figure 1 and see the first and second sentences of the article.);

b. applying a coating material having a defined thickness to the at least one wall surface, thereby causing the nano-opening to have a second cross-sectional area of nanometer-scale dimensions reduced relative to the first cross-sectional area (note the internal surfactant layer in the nanotube in Figure 1 and see the second and third paragraphs of the article).

Addressing claim 5, a hollow cylinder is implied since the solid substrate is a *nanotube*. As for the second cross-sectional area having a diameter reduced by approximately twice the coating thickness, see Figure 1.

Addressing claims 7-10, 12, 13, 15, 18 for the additional limitations of these claims see the first sentence and Figure 1 in the Lée article and Experimental Section – Electroless gold Deposition and Experimental Section – Thiol Chemisorption and Mass-Transport Measurements in Jirage ("Effect of Thiol Chemisorption on the Transport Properties of Gold Nanotube membranes," Anal. Chem. 1999, 71, 4913-1918), which was footnoted by the first sentence of Lee.

Addressing claims 36, 37, and 39, for the limitations of these claims see the first sentence of the article and Figure 1.

17. Claims 1, 5, 8, 10, 12, 36, and 37 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Ohba et al. ("N₂ Adsorption in an Internal Nanopore Space of Single-Walled Carbon Nanohorn: GCMC Simulation and Experiment," Nano Letters 2001 vol. 1, no. 7, 371-373) ("Ohaba").

Addressing claim 1, Ohba discloses a method of reducing a cross-sectional dimension of a nano-opening in a nanostructured device, comprising the steps of

a. providing a solid substrate including a nano-opening defined by at least one wall surface fabricated in the substrate, the nano-opening having a given first cross-sectional area of nanometer-scale dimensions bounded by the at least one wall surface (note the nanohorn in Figure 3 and see the second full paragraph in the first column on page 372);

b. applying a coating material having a defined thickness to the at least one wall surface, thereby causing the nano-opening to have a second cross-sectional area of nanometer-scale dimensions reduced relative to the first cross-sectional area (see the fourth full paragraph in the first column on page 372, bridging to the second column; Figure 1, and the first two images in row (A) of Figure 3 and the first image in row (B) of Figure 3).

Art Unit: 1753

Addressing claim 5, a hollow cylinder is implied since the relevant portions of the solid substrate is a *tube* and neck. See Figure 3(A) and (B). As for the second cross-sectional area having a diameter reduced by approximately twice the coating thickness, see the first two images in row (A) of Figure 3 and the first image in row (B) of Figure 3.

Addressing claim 8, for the additional limitation of this claim see the first two images in row (A) of Figure 3 and the first image in row (B) of Figure 3.

Addressing claims 10 and 12, for the additional limitation of this claim see the abstract; the first two images in row (A) of Figure 3; and the first image in row (B) of Figure 3.

Addressing claims 36 and 37 for the limitations of these claims see the abstract and Figure 3.

18. Claims 1, 7-10, 12-15, 18, and 36-39 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Chao et al. (US 6,733,828 B2) ("Chao").

Addressing claim 1, Chao discloses a method of reducing a cross-sectional dimension of a nano-opening in a nanostructured device, comprising the steps of.

a. providing a solid substrate including a nano-opening defined by at least one wall surface fabricated in the substrate, the nano-opening having a given first cross-

Art Unit: 1753

sectional area of nanometer-scale dimensions bounded by the at least one wall surface (note the mesoporous silica in Figure 1a and see col. 4:15-21);

b. applying a coating material having a defined thickness to the at least one wall surface, thereby causing the nano-opening to have a second cross-sectional area of nanometer-scale dimensions reduced relative to the first cross-sectional area (see Figures 1a and 1b and col. 4:22-64).

Addressing claims 7-14 and 18, for the additional limitations of these claims see col. 2:4-17; col. 3:54 – col. 4:30; col. 5:8 – col. 6:29; and Figure 1b.

Addressing claim 15, for the additional limitation of this claim see col. 5:8-42, especially col. 5:38-42.

Addressing claims 36-39 for the limitations of these claims see the abstract first sentence of the article and Figure 1 a and col. 5:8-42.

19. Claims 1, 2, 5, 7, 9, 12, 13, 15, 16, and 36-39 are rejected under 35 U.S.C. 102(e) as being anticipated by Pfefferle et al. (US 2003/0148086 A1) ("Pfefferle").

Addressing claim 1, Pfefferle discloses a method of reducing a cross-sectional dimension of a nano-opening in a nanostructured device, comprising the steps of

a. providing a solid substrate including a nano-opening defined by at least one wall surface fabricated in the substrate, the nano-opening having a given first cross-sectional area of nanometer-scale dimensions bounded by the at least one wall surface (see the abstract; Figure 4; paragraphs [0031], and [0043]-[0053]);

b. applying a coating material having a defined thickness to the at least one wall surface, thereby causing the nano-opening to have a second cross-sectional area of nanometer-scale dimensions reduced relative to the first cross-sectional area (see paragraphs [0066]-[0069]).

Addressing claim 2, at least one wall surface comprises three walls because the pore structures have hexagonal symmetry. At least a first width and a first depth are inherent. See paragraph [0036]. Although Pfefferle does not mention having the second cross sectional area have a width reduced by approximately twice the defined thickness this is also inherent because a the hexagonal symmetry implies three pairs of opposing side walls each side wall having a width reduced by a defined thickness. Thus, each pair of sidewalls reduce the width of the pore by two defined thicknesses.

Addressing claim 5, a continuous wall defining a hollow cylinder is shown in Figure 4 as is the second cross-sectional area having a diameter reduced by approximately twice the coating thickness.

Art Unit: 1753

Addressing claims 7, 9, 12, 13, 15, 16 for the additional limitations of these claims see Figure 4 and paragraph [0067]. For claims 15 and 16 note bovine immunoglobulin, which is a protein (polymeric polyelectrolyte)

Addressing claim 10, for the additional limitation of this claim see Figure 4.

Addressing claims 36-39 for the limitations of these claims see the abstract; Figure 4; and paragraph [0067].

Claim Rejections - 35 USC § 103

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

21. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

Art Unit: 1753

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

22. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

23. Claims 25-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guo et al. (US 203/0209314 A1) ("Guo") in view of Lee et al. ("Electromodulated Molecular Transport in Gold-Nanotube Membranes," J. AM. CHEM. Soc. 1002, 124, 11850-1851") ("Lee").

Addressing claim 25, Guo discloses a nanostructured device for use in transporting a fluid medium having components of differing lateral dimension (abstract; Figure 5; and paragraph [0002]), the device having a nanometer-scale conduit (Figure 5) and comprising a solid substrate having an upper surface (Figure 5), a nanochannel having a bottom wall spaced below the upper surface and opposed side walls (Figure 5), the nanochannel having a given first cross-sectional channel area of nanometer scale dimensions defined by the free space between the opposed side walls and the

Art Unit: 1753

depth of the bottom wall below the upper surface (Figure 5), and a planar cover member on the upper surface overlying the nanochannel, which closes the top of the channel and forms the nanometer-scale conduit (Figure 5).

Guo does not mention a coating as claimed.

Lee discloses a coating for a fluidic nanotube. See Figure 1. It would have been obvious to one with ordinary skill in the art at the time of the invention to provide a coating as taught by Lee in the invention of Guo because Guo discloses electro-osmotic flow of molecules (paragraphs [0002] and [0026]) as taught by Lee the coating can be used to control the flow of molecules through the nanometer-scale conduit. See the second full paragraph in the first column on page 11850 and Figure 1.

As for the coating material reducing the free space between the opposed sidewalls by a factor of approximately two times the defined thickness this would be inherent if a coating of approximately the same thickness (See Figure 1 of Lee) is applied to the sidewalls in Guo.

Addressing claim 26, for the additional limitations of this claim see in Guo Figure 5 and paragraph [0027].

Art Unit: 1753

Addressing claim 27, although not stated the nanochannel in Figure 5 of Guo clearly acts as a bottleneck that would affect the rate of transport of fluid medium as claimed.

Addressing claim 28, since claim 25 does not require a fluid medium, it is an intended, claim 28 does not further structurally limit claim 25 and can be rejected on the same basis as claim 25. Furthermore, the device of Guo can be used as intended by Applicants.

Addressing claims 29-32, for the additional limitations of these claims see in Lee Figure 1.

Addressing claim 33, although Figure 1 of Lee only shows a monoelectrolyte material, as recognized by Lee, "... it seems likely that more sophisticated forms of transport selectivity might be possible. For example, by making ionic versions of molecule-specific complexing agents (e.g., cyclodextrins), it might be possible to electromodulate transport of the molecules that bind to these agents." See the last paragraph of the article. Furthermore, numerous polymeric materials were used at the time of the invention as capillary coatings to control electro-osmotic flow. Thus, the use of a polyelectrolyte material in the coating just depends on the desired electromodulation of the fluid.

Art Unit: 1753

24. Claims 36-46 and 48-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Akeson et al. (US 6,746,594 B2) ("Akeson") in view of Li et al. ("Ion-beam sculpting at nanometer length scales," Nature, vol. 412, 12 July 2001) ("Li").

Akeson discloses all of the claimed limitations except for the nano-opening – in Akeson it is a micro-opening. See the abstract; Figure 1; col. 4:32 – col. 5:51; and col. 8:10 – col. 10:51. For claims 43 and 52 note that Akeson discloses alpha-hemolysin. See col. 5:45-51.

Li discloses how to make a nano-opening. See the abstract. It would have been obvious to one with ordinary skill in the art at the time of the invention to use the method of Li to make a nano-opening instead of micro-opening in the invention of Akeson because (a) the nano-opening will be more in scale with the size of a molecular assembly, such as a transmembrane channel, which may be used for sensing analytes of interest (see col. 5:37-50 in Akeson); and (b) Li states the "pores can serve to localize molecular-scale electrical junctions and switches ..." and "[w]e show that ion-beam sculpting can be used to fashion an analogous solid-state device [analogous to a cellular membrane]: a robust electronic detector consisting of a single nanopore in a Si_3N_4 membrane, capable of registering single DNA molecules in aqueous solution" (See the abstract).

25. Claim 47 is rejected under 35 U.S.C. 103(a) as being unpatentable over Akeson et al. (US 6,746,594 B2) ("Akeson") in view of Li et al. ("Ion-beam sculpting at

Art Unit: 1753

nanometer length scales," Nature, vol. 412, 12 July 2001) ("Li") as applied to claims 36-46 above, and further in view of Bloom et al. (US 6,863,833 B1) ("Bloom").

Akeson as modified by Li does not mention having the coating material modified to include a sensing agent which specifically binds the biomolecule, although a variety of possible coatings which may interact with the biomolecule are disclosed. See in Akeson col. 5:37-51.

Bloom discloses a sensing device comprising a microaperture having a coating membrane (such as a lipid bilayer as used by Akenson) and a receptor; that is a sensing agent that specifically binds to the biomolecule. See the abstract; col. 3:10-21; col. 6:29-43; and col. 7:66 – col. 8:34. The sensing device is used by exposing the biomolecule to an electrical force and measuring a change in current when the biomolecule reaches the coating. See col. 6:44-61. It would have been obvious to one with ordinary skill in the art at the time of the invention to use a sensing agent as taught by Bloom in the invention of Akeson as modified by Li because the choice of coating material from known coating materials of a similar type (e.g., lipid bilayer supported protein) will be based on the biomolecule of interest. More broadly, the choice of the active coating ingredient is just optimization of the method for the biomolecule to be measured.

Specification

26. Applicants seem to rely on an informal incorporation by reference of U.S. Patents Nos. 5,858,195 and 6,001,229 for support/explanation of for claims 54-56 (See page 13 of the specification, last paragraph); however, the examiner has not found in either patent a discussion of using electrokinetic force to coat a microchannel, let alone a nanochannel. "Mere reference to another application, patent, or publication is not an incorporation of anything therein into the application containing such reference for the purpose of disclosure as required by 35 U.S.C. 112, first paragraph. Particular attention should be directed to specific portions of the reference document where the subject matter being incorporated may be found." See MPEP 608.1(p).I.A.

27. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALEX NOGUEROLA whose telephone number is (571) 272-1343. The examiner can normally be reached on M-F 8:30 - 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, NAM NGUYEN can be reached on (571) 272-1342. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1753

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AU 1753
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